

## **REMARKS**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### **Claim Status**

Claims 3, 5, 24-32, 39-41, and 48-50 were canceled in previous amendments.

Claims 68, 69, 71 and 72 are currently amended to correct their dependencies to the appropriate claims caused by a typographical error. No new matter has been added by this amendment and Applicants request its entry.

Claims 1, 2, 4, 6, 9-23, 33-38, 42-47, and 51-72 are currently pending.

### **Amendments to the Title**

Pursuant to a request in the Office Action, Applicants have amended the title to be more descriptive. The title now identifies that the methods of the invention employ non-alpha tocopherols. Applicants submit that no new matter is presented with this amendment and hereby request its entry.

### **Rejections under 35 U.S.C. §102(e)**

At the outset, please note that Applicants hereby reiterate their arguments over this rejection that were originally presented together with the Amendment and Reply under 37 C.F.R. §1.111 filed on August 12, 2004.

**A. Claims 1, 2, 4, 6, 9-23, 33-38, 42-47, and 51-72 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent Publication 2004/0058987 to Wechter (“Wechter 2004/0058987”).**

The Claimed Invention

Applicants’ claimed invention is directed to a method for treating and/or ameliorating a symptom of neuronal damage associated with a cerebral ischemic condition in a mammalian subject by administering an effective amount of a non-alpha tocopherol enriched tocopherol composition. Previously presented claim 63, dependent on claim 1, brings out the feature that the non-alpha tocopherol component is either gamma-tocopherol, beta-tocopherol or delta-tocopherol.

The Cited Reference

Wechter 2004/0058987 was filed as a continuation application on September 12, 2003. It copied, in part, the claims of applicants’ instant application which published October 3, 2002. A comparison table is provided below:

<b>Applicants’ Original Claim filed 12/14/2002</b>	<b>Claim in Wechter 2004/0058987 filed 9/12/2003</b>
1	1
2	2
3 <sup>1</sup>	3
8 <sup>2</sup>	4
9	5
10	6
15	7
16	8

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<sup>1</sup> Canceled by previous amendment.

<sup>2</sup> Canceled by previous amendment; note that 6-hydroxy-2,7,8-trimethylchroman-2-propanoic acid (LLU-α) is the same as gamma-CEHC (see, e.g., page 14, lines 19-25 of the instant specification).

<b>Applicants' Original Claim filed 12/14/2002</b>	<b>Claim in Wechter 2004/0058987 filed 9/12/2003</b>
17	9
18	10
22	13
51	15
52	16
53	17
54	18

The specification of Wechter 2004/0058987 describes the use gamma-tocopherol and its metabolite LLU- $\alpha$  (gamma-CEHC) to treat a number of conditions: “high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathological lesions and a reduced immune system response...” (Paragraph [0008]); “producing a natriuretic effect” (Paragraph [0009]); “cardiovascular diseases such as ischemia, angina, edematous conditions, atherosclerosis, LDL-oxidation, adhesion of monocytes to endothelial cells, foam cell formation, fatty-streak development, platelet adherence, platelet aggregation, smooth muscle cell proliferation, and reperfusion injury....treat and prevent cancers such as lung cancer, prostate cancer, breast cancer, and colon cancer...” (Paragraph [0011]); “treatment and prevention of natriuretic diseases, such as hypertension, high blood pressure, ischemia, angina pectoris, congestive heart failure, cirrhosis of the liver, nephritic syndrome, ineffective renal perfusion or ineffective glomerular filtration....neurological diseases including hyporeflexia, ophthalmoplegia, and axonal dystrophy... improve a subject’s immune system response, reduce the production of free radicals...” (Paragraph [0012]); “natriuretic diseases [meaning] disease associated with abnormal excretion of sodium from the body...hypertension, high blood pressure, ischemia, angina pectoris, congestive heart failure, cirrhosis of the liver, nephritic syndrome, ineffective renal perfusion, and ineffective glomerular filtration” (Paragraph [0018]).

While, as described above, the specification of Wechter 2004/0058987 describes the use of gamma-tocopherol for treating a variety of diseases, nowhere in the specification of Wechter 2004/0058987 is the term “cerebral ischemic condition” used. Nor does the specification Wechter 2004/0058987 describe a method for treating and/or ameliorating a symptom of neuronal damage associated with a cerebral ischemic condition in a mammalian subject by administering an effective amount of a non-alpha tocopherol enriched tocopherol composition. Comparison with parent application(s) reveals that the claims directed to such treatment were added in the present application as of its filing date of September 12, 2003 and that most of these claims<sup>3</sup> appear to be copied from applicants’ previously published applications.<sup>4</sup>

### Analysis

In order to qualify as a prior art reference under 35 U.S.C. §102(e), the reference patent or patent publication must have a filing date that is earlier than the effective filing date of the application under examination. MPEP § 706.02(a). To sustain a rejection under 35 U.S.C. §102(e), the invention must have been described in application for patent by another filed in the U.S. (or in an international patent application designating the U.S. under 35 U.S.C. §351(a)) before the invention by the applicants.

### **1. The claims of Wechter 2004/0058987 are not supported by the disclosure of the specification.**

As stated above, in order to sustain a rejection under 35 U.S.C. §102(e), the invention must have been described in application for patent by another filed in the U.S. (or in an international patent application designating the U.S. under 35 U.S.C. §351(a)) before the invention by the applicants.

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<sup>3</sup> Wechter’s claims 11, 12, 14 and 19 recite variations or slightly different (but overlapping) ranges of claims presented by the instant application.

<sup>4</sup> The instant application published as U.S. Publication 2004/0143049 on October 3, 2002; a corresponding PCT application published as WO 0247680 on June 20, 2002.

Although Wechter 2004/0058987 claims priority to earlier filed continuation applications, the specification on which Wechter 2004/0058987 is based does not support its claims, as detailed above. Accordingly, the claims and the subject matter thereof cannot derive benefit of the earlier filing date(s). Thus, since the filing date of Wechter 2004/0058987 is later than both the filing date and the priority dates of the applicants' instant application, the Wechter claim subject matter cited by the Examiner against the applicants' instant claims cannot be said to anticipate the applicants' claimed invention under 35 U.S.C. §102(e).

**2. Rejection under 35 U.S.C. §102(e) is improper.**

Furthermore, a rejection under 35 U.S.C. §102(e) is improper if the Examiner believes that the claims of Wechter 2004/0058987 are identical to the claims of the instant application. In such instances, the Examiner must determine whether a double patenting rejection or an interference is appropriate. MPEP 706.02(b). In the current case, there is no support in the specification for the claims as filed in Wechter 2004/0058987. Rather it appears that Wechter 2004/0058987 has copied the applicants' original claims, as detailed in the table above.

In view of the foregoing, applicants submit that Wechter 2004/0058987 is not an effective reference against the applicants' pending claims. Accordingly, withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Applicants acknowledge, with thanks, that the Examiner has agreed to obtain all of the Wechter applications for review to assess Applicants' arguments. Applicants look forward to the Examiner's assessment. In the meantime, Applicants maintain the arguments previously presented.

**B. Claims 1, 2, 4, 6, 9-23, 33-38, 42-47 and 51-72 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent Publication 2004/0058986 to Wechter (“Wechter 2004/0058986”).**

The Claimed Invention

The applicant’s claimed invention is described under Part A of this section, above.

The Cited Reference

Applicants believe that the specification of Wechter 2004/0058986 is identical to the specification of Wechter 2004/0058987, as described under Part A of this section, above.

For what appears to be the first time in the line of applications in the patent family that encompasses Wechter 2004/0058986, applicant Wechter introduces the concept of the use of gamma-tocopherol to treat “non-cardiovascular tissue ischemia” into the claims of the application as filed on September 12, 2003. The term “non-cardiovascular tissue ischemia” was not used in the specification.

The Examiner further cited the claims of Wechter 2004/0058986 for its recitation of treatment of spinal cord ischemia, peripheral nerve damage and neuropathies. While the specification describes administration of gamma-tocopherol and LLU- $\alpha$  to Vitamin E deprived mice susceptible to developing neuropathic lesions as a consequence of such deprivation, Applicants submit that the Wechter specification does not support treatment of spinal cord ischemia, peripheral nerve damage and neuropathies, along the lines of the present invention.

Analysis

**1. The claims of Wechter 2004/0058986 are not supported by the disclosure of the specification.**

As stated above, in order to sustain a rejection under 35 U.S.C. §102(e), the invention must have been described in application for patent by another filed in the U.S. (or in an

international patent application designating the U.S. under 35 U.S.C. §351(a)) before the invention by the applicants.

Although Wechter 2004/0058986 claims priority to earlier filed continuation applications, the specification on which Wechter 2004/0058986 is based does not provide support for its current claims, as described above. Accordingly, the claims and the subject matter thereof cannot derive benefit of the earlier filing date(s). Thus, since filing date of Wechter 2004/0058986 is later than both the filing date and the priority dates of the applicants' instant application, the subject matter of Wechter 2004/0058986 that the Examiner has cited against the instant claims cannot be said to anticipate the applicants' claimed invention under 35 U.S.C. §102(e).

**2. Rejection under 35 U.S.C. §102(e) is improper.**

Furthermore, a rejection under 35 U.S.C. §102(e) is improper if the Examiner believes that the claims of Wechter 2004/0058986 are identical to the claims of the instant application. In such instances, the Examiner must determine whether a double patenting rejection or an interference is appropriate. MPEP 706.02(b). In the current case, there is no support in the specification for the claims as filed in Wechter 2004/0058986.

In view of the foregoing, applicants submit that Wechter 2004/0058986 is not an effective reference against the applicants' pending claims. Accordingly, withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

Applicants again acknowledge, with thanks, that the Examiner has agreed to obtain all of the Wechter applications for review to assess Applicants' arguments. Applicants look forward to the Examiner's assessment. In the meantime, Applicants maintain the arguments previously presented.

**Rejection under 35 U.S.C. §103(a)**

Claims 1-64 and 98 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Wechter, W.J., U.S. 2004/0029954 (“Wechter 2004/0029954”). It is the Examiner’s position that the claims of Wechter 2004/0029954, which recite “methods of treating or preventing any ischemic condition comprising administering a composition comprising tocopherols, at least 50% of which being  $\gamma$ -tocopherol” render obvious the applicants’ claimed invention. The Examiner further asserts that it would have been reasonable to expect an improvement in an ischemic condition of the brain, i.e., an improvement in blood supply to the brain, would result in a reduction of neuronal damage associated with ischemia.

Applicants hereby reiterate their arguments over this rejection that were originally presented together with the Amendment and Reply under 37 C.F.R. §1.111 filed on August 12, 2004. Applicants also include new arguments over this rejection.

The Claimed Invention

Claims 1, 2, 4, 6, 9-23, 33-38, 42-47 and 51-72 are pending in the application. As currently claimed, the invention is directed to methods of treating and/or ameliorating a symptom of neuronal damage associated with a cerebral ischemic condition in a mammalian subject by administering an effective amount of a non-alpha tocopherol enriched tocopherol.

The Cited Reference

Wechter 2004/0029954 was filed on February 21, 2003 and claims priority via a series of continuation applications to December 17, 1998. Except for the claims, applicants submit that the specification of Wechter 2004/0029954 is essentially identical to that of Wechter 2004/0058987 and Wechter 2994/0058987, described above. As stated above, while the specification of Wechter 2004/0029954 describes a whole “laundry list” of maladies, it does not describe or support the subject matter of the claims set forth in the Wechter’s application as filed on February 21, 2003, which form the basis for the Examiner’s rejection under this section.



Analysis

**1. Wechter 2004/0029954 is not an effective reference against the instant application for the subject matter cited by the Examiner.**

As stated above, the subject matter of Wechter 2004/0029954 that the Examiner cites against the applicants' claimed invention is not supported by the specification and therefore does not derive the benefit of the earlier filing date(s). Specifically, the filing date of Wechter 2004/0029954 is later than both the filing date and the priority dates of the applicants' instant application, the cited subject matter of Wechter 2004/0029954 cannot be said to render obvious the applicants' claimed invention.

**2. Wechter 2004/0029954 does not render obvious the claimed subject matter of the instant application.**

The subject matter of the specification of Wechter 2004/0029954 is described in the previous section. To re-iterate, Wechter 2004/0058986 describes the use of gamma-tocopherol, to treat a number conditions: "high blood pressure, thromboembolic disease, cardiovascular disease, cancer, natriuretic disease, the formation of neuropathological lesions and a reduced immune system response..." (Paragraph [0008]); "producing a natriuretic effect" (Paragraph [0009]); "cardiovascular diseases such as ischemia, angina, edematous conditions, atherosclerosis, LDL-oxidation, adhesion of monocytes to endothelial cells, foam cell formation, fatty-streak development, platelet adherence, platelet aggregation, smooth muscle cell proliferation, and reperfusion injury....treat and prevent cancers such as lung cancer, prostate cancer, breast cancer, and colon cancer" (Paragraph [0011]); "treatment and prevention of natriuretic diseases, such as hypertension, high blood pressure, ischemia, angina pectoris, congestive heart failure, cirrhosis of the liver, nephritic syndrome, ineffective renal perfusion or ineffective glomerular filtration....neurological diseases including hyporeflexia, ophthalmoplegia, and axonal dystrophy... improve a subject's immune system response, reduce the production of free radicals..." (Paragraph [0012]); "natriuretic diseases [meaning] disease associated with abnormal excretion of sodium from the body...hypertension, high blood pressure, ischemia,

angina pectoris, congestive heart failure, cirrhosis of the liver, nephritic syndrome, ineffective renal perfusion, and ineffective glomerular filtration” (Paragraph [0018]).

### Analysis

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) (MPEP 2143).

While the specification of Wechter 2004/0029954 suggests the use of gamma-tocopherol for a whole plethora of indications, as described above, these indications do not include the category of cerebral ischemic conditions. Nor is there anything in the reference that would suggest that its teachings of the treatment of the various enumerated disease states might also be applicable to treating non-cardiovascular tissue ischemias.

Applicants again submit that the Examiner's assertion that it would have been reasonable to expect that an improvement in blood supply to the brain would result in a reduction of neuronal damage associated with ischemia also lacks basis in the specification or in objective reality. While Wechter 2004/0029954 describes increased natriuresis, it is commonly accepted that this is associated with increased perfusion of the *kidney*; any effects on blood flow to the brain are purely speculative and without evidential basis.

Even if the natriuretic effect was associated with increased blood flow to the brain, any increased blood flow to the brain can, in fact, cause irreversible neuronal damage.

Regardless of the teachings of the Merck Manual supplied by the Examiner, Applicants submit that it is well known in the art that when a patient suffers from ischemia and then undergoes reperfusion, reperfusion injury occurs. This reperfusion injury can cause *irreversible* damage to the neuronal cells. *See, e.g.* Oliver, C. N., et al. *Proc. Natl. Acad. Sci. USA*, 87:5144-5147 (1990) (enclosed herewith); Islekel, H., et al. *Norol. Bil. D*, 17(2), #20 (2000) (abstract)(enclosed herewith); Matsumoto, T., et al., *Lab. Invest.* 77(2):119-125 (1997)(abstract)(enclosed herewith); Namura, S., et al., *Proc. Natl. Acad. Sci. USA*, 98(20):11569-11574 (2001)(abstract)(enclosed herewith). In light of this potential irreversible damage, Applicants maintain that an improvement in blood supply to the brain would not necessarily result in a reduction of neuronal damage but rather cause more neuronal damage. That is to say that there can be no reasonable expectation of success.

Since the Wechter 2004/0029954 neither shows nor suggests methods of treating cerebral ischemic conditions, along the lines of the applicants' claimed invention, it cannot be said to render obvious the instant invention. Accordingly, reconsideration and withdrawal of the rejection of the claims over Wechter 2004/0029954 is respectfully requested.

Applicants again acknowledge, with thanks, that the Examiner has agreed to obtain all of the Wechter applications for review to assess Applicants' arguments. Applicants look forward to the Examiner's assessment. In the meantime, Applicants maintain the arguments previously presented.

#### **Rejection under Judicially Created Doctrine of Obviousness-type Double Patenting**

Claims 1, 2, 4, 6, 9-23, 33-38, 42-47 and 51-62 currently stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 2, 11-13, 22, 31-33, 42, 53-57 and 98 of co-pending application USSN: 10/017,717. As the Examiner has noted, Applicants have requested that this rejection be held in abeyance until the claims of one of the applications are deemed in condition for allowance.

**Conclusion**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date February 9, 2005

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